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DIALYSIS – TRANSPLANTATION

Prognostic value of 24-hour ambulatory blood pressure monitoring and of night/day ratio in nondiabetic, cardiovascular events–free hemodialysis patients

GIOVANNI TRIPEPI, RICCARDO MARIA FAGUGLI, PIETRO DATTOLO, GIOVANNA PARLONGO, FRANCESCA MALLAMACI, UMBERTO BUONCRISTIANI, and CARMINE ZOCCALI

CNR-IBIM, Clinical Epidemiology and Physiopathology of Renal Disease and Hypertension, Reggio Cal, Italy; Nephrology-Dialysis Department, Ospedale Silvestrini, Perugia, Italy; and Dialysis and Nephrology Unit, S.M. Annunziata Hospital, Florence, Italy

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Background. The use of 24-hour ambulatory blood pressure monitoring is increasing in end-stage renal disease (ESRD) patients but the prediction power for cardiovascular complications of time-averaged ambulatory blood pressure components has been little investigated in these patients.

Methods. We analyzed the prognostic power of 24-hour ambulatory blood pressure monitoring for all-cause and cardiovascular mortality in 168 nondiabetic, events-free hemodialysis patients selected from a total dialysis population of about 450 patients.

Results. During the follow-up period (38 ± 22 months), 48 patients died, 29 of them of cardiovascular causes. On univariate Cox regression analyses, the night/day systolic ratio resulted to be the sole blood pressure indicator to be associated with all-cause and cardiovascular mortality while left ventricular hypertrophy (LVH) was a strong predictor of these outcomes. In multivariable Cox models not including LVH, the night/day systolic ratio maintained an independent prognostic value for incident outcomes. However, when both risk factors, LVH and night/day systolic ratio, were introduced into Cox models, LVH was no longer a significant predictor while the night/day systolic ratio became a predictor of marginal statistical significance.

Conclusion. The night/day ratio emerges as the sole ambulatory blood pressure monitoring–derived indicator providing significant prognostic information in patients with ESRD. However, this indicator as well as LVH loses substantial prediction power in statistical models including both risk factors. The results suggest that the night/day systolic ratio and LVH provide overlapping prognostic information, a phenomenon in keeping with the hypothesis that they represent a common pathway leading to adverse outcomes in ESRD.

Key words: ambulatory blood pressure monitoring, dialysis, cardiovascular risk, left ventricular hypertrophy.

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The relationship between arterial pressure and cardiovascular outcomes is perhaps one of the most intriguing and controversial issues in renal medicine [1]. While in the general population without cardiovascular complications there is a direct, strong relationship between blood pressure and incident cardiovascular events [2–4], in dialysis patients either no or inverse relationships have been reported in very large dialysis cohorts [5–9]. This apparently paradoxic phenomenon, which was lucidly described in a seminal study by Foley et al [10], is currently interpreted as an expression of the inverse epidemiology of this population [11, 12]. However, to date there is no study directly addressing the hypothesis that hypertension triggers cardiovascular events via left ventricular hypertrophy (LVH) [10]. According to this hypothesis, LVH generated by hypertension causes heart failure which transforms the blood pressure cardiovascular events relationship from a direct into an inverse one, hypotension being eventually a marker of pump failure. Testing this hypothesis would demand enrolment of patients without cardiovascular complications and without pronounced alterations in left ventricular mass at baseline, as well as precise assessment of the blood pressure burden. Since LVH is pervasive in the dialysis population (prevalence rate 80%) selecting hemodialysis patients without LVH is a costly and lengthy approach posing objective enrolment difficulties. We thought that the problem could be pragmatically approached by collecting reliable estimates of blood pressure load (24-hour ambulatory blood pressure monitoring) [13] in a well-selected study population composed by individuals at low baseline cardiovascular risk.

With this background in mind, in 1994 we started a multicenter cohort study investigating the relationship between 24-hour ambulatory blood pressure monitoring components and cardiovascular outcomes in nondiabetic, cardiovascular events–free, hemodialysis patients

without clinical evidence of heart failure at enrollment. This is the largest 24-hour ambulatory blood pressure monitoring study in dialysis patients performed so far and the sole prospective study investigating the relationship between 24-hour ambulatory blood pressure monitoring and mortality and incident cardiovascular events in a selected cohort composed by low-risk dialysis patients. To circumvent the confounding effect of baseline left ventricular mass we modeled the influence of LVH on survival by multivariate analysis. Of note, this particular study setting was also ideally suited for testing whether alterations in circadian blood pressure control trigger cardiovascular events in this population, a possibility suggested by small studies in unselected patients [14, 15] and by some cross-sectional observations [16, 17].

METHODS

Protocol

The protocol was in conformity with the ethical guidelines of our institutions and informed consent was obtained from each participant.

Study cohort

Patients were enrolled in three dialysis units (Reggio Calabria, Firenze, and Perugia). For the selection criteria adopted for this study, patients had to be nondiabetic and cardiovascular events–free and without a history or clinical evidence of heart failure. Heart failure was defined pragmatically as suggested by Foley (i.e., dyspnea in addition to two of the following conditions, raised jugular pressure, bibasilar crackles, pulmonary venous hypertension, or interstitial edema on chest x-ray films, requiring hospitalization or extra ultrafiltration) [18]. From a whole dialysis population of about 450 individuals, 168 patients (85 males and 83 females) met the enrollment criteria. These patients had been on regular hemodialysis treatment for a median time of 54 months (interquartile range 19 to 76 months).

Patients were being treated three times a week with standard bicarbonate dialysis (sodium 138 mmol/L, HCO_3 35 mmol/L, potassium 1.5 mmol/L, calcium 1.25 mmol/L, andMg 0.75 mmol/L) by cuprophan or semisynthetic membranes. Dry weight was targeted in each case to achieve a normotensive edema-free state. The average urea Kt/V in these patients was 1.21 ± 0.24. Forty patients were habitual smokers and 89 patients were on treatment with erythropoietin. Ninety patients were on antihypertensive therapy [49 on monotherapy with angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, beta-blockers, sympathicolitic agents, diuretics, and vasodilators and 41 on double ($N = 28$), triple ($N = 11$), or quadruple ($N = 2$) therapy with various combinations of these drugs]. The main demographic and clinical characteristics of the study population are summarized in Table 1 (first column).

Follow-up study

After the initial assessment patients were followed up for an average time of 38 ± 22 months (range 1.7 to 98.5 months). During the follow-up period fatal cardiovascular events and death were accurately recorded. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death, family members were interviewed by telephone to better ascertain the circumstances surrounding death.

24-hour ambulatory blood pressure monitoring

Twenty-four–hour ambulatory blood pressure monitoring was performed during a nondialysis day by using two devices conforming to the AAMI recommendations (Takeda 2420 modification 7) Takeda, Tokyo, Japan) (Spacelabs 90207) (Redmond, WA, USA). All 24-hour ambulatory blood pressure monitoring recordings were carried out every 15 minutes both during the day (07:00 a.m. to 11:00 p.m.) and during the night (11:00 p.m. to 07:00 a.m.). The cuff was placed on the nonfistula arm and the patients were instructed to maintain their usual level of activity. Twenty-four–hour ambulatory blood pressure monitoring data were stored on personal computers. Blood pressure readings were printed out for direct inspection and edited according to a well-established protocol [19].

We tested by the Bland-Altman method [20] the reproducibility of the night/day systolic ratio in 19 patients who underwent 48-hour ambulatory blood pressure monitoring in 2 consecutive days (dialysis interval and dialysis day).

Predialysis blood pressure

Predialysis blood pressure was calculated as the average value of 12 recordings (three/week) taken by the nurses immediately before dialysis during the month preceding the study [17].

Definitions

As an indicator of night day arterial pressure fall we considered the night/day systolic ratio (i.e., the ratio of the average value of systolic pressure during the night (11:00 p.m. to 7:00 a.m.) and the corresponding average value of systolic pressure during the day (07:00 a.m. to 11:00 p.m.). We elected to use this ratio than the night-day blood pressure fall because this ratio is less dependent on absolute blood pressure values than the night-day blood pressure fall [21]. Diagnosis of 24-hour ambulatory blood

Table 1. Main demographic, somatometric, clinical and biochemical characteristics of patients included in the study

		Night/day systolic ratio			
	Whole group	I tertile (<0.93)	II tertile (0.94-1.01)	III tertile (>1.01)	*P* for trend
Age *years*	57.2 ± 15.8	55.9 ± 16.2	58.2 ± 15.9	57.4 ± 15.7	0.64
Male gender%	51	49	55	47	0.84
Smokers%	24	27	18	28	0.80
Duration of regular hemodialysis treatment *months*	54 (19–76)	45 (16–73)	55 (28–74)	62 (16–104)	0.59
On anti-hypertensive therapy%	54	47	53	60	0.19
24-hour arterial pressure *mm Hg*					
Systolic pressure	141.0 ± 25.4	130.4 ± 24.6	145.9 ± 23.8	144.6 ± 25.5	0.004
Diastolic pressure	78.0 ± 13.1	74.1 ± 11.6	80.6 ± 13.9	78.6 ± 12.9	0.07
Pulse pressure	62.9 ± 19.1	56.4 ± 18.5	65.3 ± 17.8	66.0 ± 19.9	0.01
Diurnal arterial pressure (7.00–22.00) *mm Hg*					
Systolic pressure	141.7 ± 24.9	134.9 ± 24.8	147.6 ± 23.8	141.1 ± 25.1	0.20
Diastolic pressure	79.3 ± 13.5	76.2 ± 12.2	82.5 ± 13.9	78.4 ± 13.5	0.40
Pulse pressure	62.4 ± 18.9	58.6 ± 18.9	65.1 ± 18.2	62.7 ± 19.5	0.27
Nocturnal arterial pressure (22.00–7.00) *mm Hg*					
Systolic pressure	138.3 ± 28.6	117.3 ± 23.8	142.7 ± 22.6	151.6 ± 28.3	<0.001
Diastolic pressure	74.9 ± 14.1	67.5 ± 11.6	77.2 ± 14.3	78.9 ± 13.4	<0.001
Pulse pressure	63.4 ± 21.5	49.8 ± 16.9	65.5 ± 18.1	72.7 ± 22.7	<0.001
Predialysis blood pressure *mm Hg*					
Systolic pressure	145.0 ± 18.2	139.3 ± 21.0	149.0 ± 15.8	145.6 ± 17.1	0.07
Diastolic pressure	80.0 ± 10.2	77.6 ± 11.1	81.8 ± 8.6	80.0 ± 10.8	0.24
Pulse pressure	65.1 ± 13.3	61.7 ± 14.2	67.2 ± 13.2	65.6 ± 12.4	0.13
Hematocrit%	30.8 ± 5.3	31.0 ± 5.4	31.7 ± 5.0	29.6 ± 5.4	0.16
Albumin *g/L*	41.1 ± 6.4	42.7 ± 3.9	40.3 ± 7.8	40.8 ± 6.1	0.19
Cholesterol *mmol/L*	4.96 ± 1.42	4.84 ± 1.13	5.01 ± 1.68	5.00 ± 1.33	0.62
Calcium ∗ phosphate $mmol^2/L^2$	4.59 ± 1.18	4.35 ± 1.01	4.48 ± 1.27	4.92 ± 1.16	0.01
Kt/V	1.21 ± 0.25	1.18 ± 0.23	1.20 ± 0.26	1.24 ± 0.25	0.25
Left ventricular hypertrophy%	72	63	73	81	0.03
Incident events					
Deaths number (%)	48 (29%)	7 (14%)	19 (31%)	22 (39%)	0.006
Cardiovascular deaths number (%)	29 (60% of total deaths)	2 (4%)	11 (18%)	16 (28%)	0.001

Data are reported as mean ± SD, median and interquartile range or as percent frequency, as appropriate.

pressure monitoring hypertension was done according to the threshold of 129/79 mm Hg that corresponds to an office blood pressure of 140/90 mm Hg [22].

Echocardiography

Echocardiography was performed according to a well-standardized protocol [23]. LVH was defined by a left ventricular mass index of over 47 $g/m^{2.7}$ in women or over 50 $g/m^{2.7}$ in men.

Statistical analysis

Data are reported as mean ± SD, median and interquartile range or as percent frequency, as appropriate and the comparison among groups were made by *P* for trend.

The prognostic value for all-cause and cardiovascular mortality of 24-hour ambulatory blood pressure monitoring and of night/day systolic ratio was analyzed by univariate and multivariate Cox's regression analysis. As potential confounders we considered a set of well-established risk factors in dialysis patients: age, gender, smoking, duration of regular hemodialyis treatment, antihypertensive therapy, hematocrit, albumin, cholesterol, calcium phosphate product, fractional urea clearance (Kt/V), and LVH. In a first step we identified all covariates that were significantly associated to all-cause and cardiovascular mortality with $P < 0.05$ at univariate Cox regression analysis. After the definition of basic models of prognostic variables we tested the predictive power of the night/day systolic ratio in multivariate Cox's models, including all univariate predictors of all-cause and cardiovascular death. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis.

The usefulness of night/day systolic ratio and LVH to predict incident all cause and cardiovascular mortality was also tested by the analysis of receiver operating characteristic (ROC) curves [24]. All calculations were done using a standard statistical package (SPSS for Windows, version 9.0.1, 1999).

Table 2. Causes of death in the study cohort

	Number
Cardiovascular	
Myocardial infarction	9
Sudden death	7
Stroke	5
Pulmonary embolism	3
Heart failure	2
Mesenteric infarction	2
Arrhythmia	1
Other causes	
Sepsis/Infection	5
Neoplasia	5
Gastrointestinal hemorrhage	3
Cachexia	3
Hyperkalemia	1
Multiple myeloma	1
Liver cirrhosis	1

RESULTS

Twenty-four–hour systolic hypertension was more frequent ($N = 118$) (70%) than diastolic hypertension ($N = 74$) (44%) and the night/day systolic ratio was ≥ 1 in 59 out of 168 dialysis patients (i.e., 35%). As shown in Table 1, both systolic and diastolic blood pressures showed a minimal reduction during night-time in comparison to daytime (−3.4 mm Hg and −4.4 mm Hg, respectively).

Prognostic value of 24-hour ambulatory blood pressure monitoring and other risk factors: Univariate analyses

During the follow-up period (38 ± 22 months, range 1.7 to 99.0 months), 48 patients died, 29 of them (i.e., 60% of total deaths) of cardiovascular causes (Table 2). The prognostic value of blood pressure measurements for all-cause and cardiovascular mortality was assessed by dividing patients into three tertiles according to individual ambulatory blood pressure components. As shown in Table 3, on univariate Cox regression analysis, neither 24-hour ambulatory blood pressure nor day or night ambulatory blood pressures were significantly associated to all-cause and cardiovascular mortality. The night/day systolic ratio was the sole blood pressure indicator to be associated with all-cause death (Table 3) and the association between this factor and cardiovascular mortality appeared particularly strong because patients in the third tertile of night/day systolic ratio had a risk of cardiovascular death that was 6.89 times higher than those in the first tertile (Table 3). The strong link between the night/day systolic ratio and cardiovascular mortality was also fully evident when the analysis was carried out on continuous data [HR (1% increase in night/day systolic ratio) 1.05, 95% CI 1.01-1.08, $P = 0.008$].

Analyses considering blood pressure components as continuous variables did not materially differ from those based on blood pressure tertiles. Because night/day systolic ratio emerged as the sole significant blood pressure–derived marker to be associated with all-cause and cardiovascular mortality, further data analysis was restricted only to this parameter. Of note also LVH (all-cause death HR 4.30, 95% CI 1.70-10.90; cardiovascular death HR 6.81, 95% CI 1.61-28.74, $P \leq 0.009$) and smoking (all-cause death HR 2.62, 95% CI 1.41-4.86; cardiovascular death HR 4.86, 95% CI 2.29-10.30, $P \leq 0.002$) emerged as strong univariate predictors of all-cause and cardiovascular mortality. Age [HR (1-year increase) 1.05, 95% CI 1.02-1.07, $P < 0.001$] and serum cholesterol [HR (1 mmol/L increase) 0.73, 95% CI 0.56-0.95, $P = 0.02$] were significantly associated to all-cause mortality while serum albumin [HR (1 g/L increase) 0.94, 95% CI 0.90-0.97, $P < 0.001$] was strongly and inversely associated to cardiovascular death. There was no center effect both for all-cause and cardiovascular mortality. Predialysis blood pressure components (systolic, diastolic, and pulse pressure) failed to predict both all-cause (P ranging from 0.40 to 0.63) and cardiovascular mortality (P ranging from 0.19 to 0.56).

Table 3. Univariate Cox regression of 24-hour ambulatory blood pressure monitoring (tertiles) for all-cause and cardiovascular mortality

All cause mortality	HR and 95% CI (III vs. I tertile)	P value
All-cause mortality 24-hour blood pressure		
Systolic pressure	0.92 (0.47-1.81)	0.80
Diastolic pressure	1.05 (0.53-2.09)	0.88
Pulse pressure	1.03 (0.51-2.08)	0.93
Diurnal blood pressure		
Systolic pressure	1.00 (0.51-1.94)	0.99
Diastolic pressure	0.77 (0.39-1.56)	0.47
Pulse pressure	1.05 (0.51-2.17)	0.89
Nocturnal blood pressure		
Systolic pressure	1.18 (0.58-2.40)	0.64
Diastolic pressure	1.08 (0.55-2.12)	0.83
Pulse pressure	1.54 (0.74-3.19)	0.24
Night/day systolic ratio	2.66 (1.13–6.25)	0.03
Cardiovascular mortality		
24-hour blood pressure		
Systolic pressure	1.20 (0.47-3.02)	0.71
Diastolic pressure	1.79 (0.66-4.86)	0.25
Pulse pressure	1.50 (0.59-3.80)	0.40
Diurnal blood pressure		
Systolic pressure	1.29 (0.55-3.06)	0.56
Diastolic pressure	0.88 (0.31-2.48)	0.80
Pulse pressure	1.37 (0.52-3.57)	0.52
Nocturnal blood pressure		
Systolic pressure	2.30 (0.77-6.87)	0.14
Diastolic pressure	1.79 (0.68-4.72)	0.24
Pulse pressure	2.61 (0.99-6.89)	0.06
Night/day systolic ratio	6.89 (1.58-30.10)	0.01

Data are expressed as hazard ratio (95% CI) and P values.

Correlates of night/day systolic ratio

As shown in Table 1, patients in the third tertile of night/day systolic ratio had higher 24-hour average

Table 4. Multivariate Cox regression analysis for all-cause and cardiovascular mortality

		Model not including left ventricular hypertrophy		Model including left ventricular hypertrophy	
	Units of increase	HR and 95% CI	*P* value	HR and 95% CI	*P* value
All-cause mortality					
Age	1 year	1.04 (1.02–1.07)	0.001	1.04 (1.01–1.07)	0.01
Smoking	0, no; 1, yes	3.61 (1.88–6.94)	<0.001	3.35 (1.73–6.47)	<0.001
Cholesterol	1 mmol/L	0.73 (0.56–0.95)	0.02	0.75 (0.57–0.98)	0.04
Night/day ratio					
I tertile	<0.93	1[a]		1[a]	
II tertile	0.94–1.01	2.37 (0.98–5.70)	0.05	2.09 (0.85–5.13)	0.11
III tertile	>1.01	2.88 (1.21–6.87)	0.02	2.52 (1.03–6.15)	0.04
Left ventricular hypertrophy	0, no; 1, yes			1.81 (0.64–5.09)	0.26
Cardiovascular mortality					
Age	1 year	1.03 (0.99–1.07)	0.07	1.02 (0.98–1.06)	0.31
Smoking	0, no; 1, yes	6.90 (3.08–15.43)	<0.001	6.37 (2.83–14.33)	<0.001
Albumin	1 g/L	0.93 (0.89–0.97)	0.001	0.93 (0.89–0.97)	0.001
Night/day ratio					
I tertile	<0.93	1[a]		1[a]	
II tertile	0.94–1.01	3.59 (0.76–16.9)	0.11	2.89 (0.61–13.72)	0.18
III tertile	>1.01	5.73 (1.28–25.56)	0.02	4.33 (0.96–19.61)	0.06
Left ventricular hypertrophy				3.56 (0.76–16.66)	0.11

[a]Reference group.
Data are expressed as hazard ratio (HR) and 95% confidence interval (CI).

systolic and pulse pressure and calcium ∗ phosphate product and higher prevalence of LVH than patients in the other two tertiles. Diurnal ambulatory blood pressure values as well as predialysis blood pressure components did not differ in the three tertiles of night/day systolic ratio. However, there was a highly significant, graded increase in all nocturnal blood pressure components across the three tertiles.

Prognostic value of night/day systolic ratio and LVH: Multivariable and ROC curve analyses

In multivariate Cox models, including all univariate predictors of all-cause and cardiovascular death but LVH, the night/day systolic ratio maintained an independent prognostic power for these outcomes (Table 4). However, when we introduced LVH into the multivariable models, this risk factor was no longer a significant predictor while the night/day systolic ratio became a predictor of marginal statistical significance (Table 4). When analyzed with the ROC curve approach, the night/day systolic ratio and LVH had very close predictive power and the gain in prediction power which could be obtained by jointly considering the two risk factors was of modest degree (+5% both for all-cause and cardiovascular mortality) (see Fig. 1). Collectively, these results suggest that the night/day systolic ratio and LVH provide overlapping prognostic information, a phenomenon suggesting that they, at least in part, represent a common pathway leading to adverse outcomes. In keeping with this hypothesis there was a graded relationship between the prevalence of LVH and night/day systolic ratio and predialysis systolic blood pressure, an association also present with day and night systolic blood pressures (Fig. 2).

Night/day systolic ratio reproducibility

The reproducibility of the night/day systolic ratio was tested in patients who underwent 48-hour ambulatory blood pressure monitoring in 2 consecutive days (dialysis interval and dialysis day). In these patients the night/day systolic ratio resulted to be a satisfactorily reproducible measurement because no point exceeded the two SD in the Bland-Altman graph (Fig. 3).

DISCUSSION

In a low-risk cohort of 168 nondiabetic hemodialysis patients without heart failure and without background cardiovascular complications the night/day systolic ratio emerged as the sole blood pressure indicator to be associated to all-cause and cardiovascular mortality and its prognostic value for these outcomes was largely dependent on LVH. Furthermore, no diurnal or nocturnal 24-hour ambulatory blood pressure components as well as predialysis blood pressure resulted to be significantly related to all-cause and cardiovascular mortality.

Study cohort

Due to the high frequency of diabetes, heart failure, and background cardiovascular complications (the exclusion criteria of this study) we could select just about one third of patients of a large dialysis population ($N = 450$). Such an exclusion process is fundamental for minimizing the effect of the "inverse epidemiology" phenomenon (i.e., the phenomenon whereby advanced cardiovascular disease and heart failure lead to hypotension and death). The selection process applied to our population was well reflected in the relatively low mortality rate of our cohort

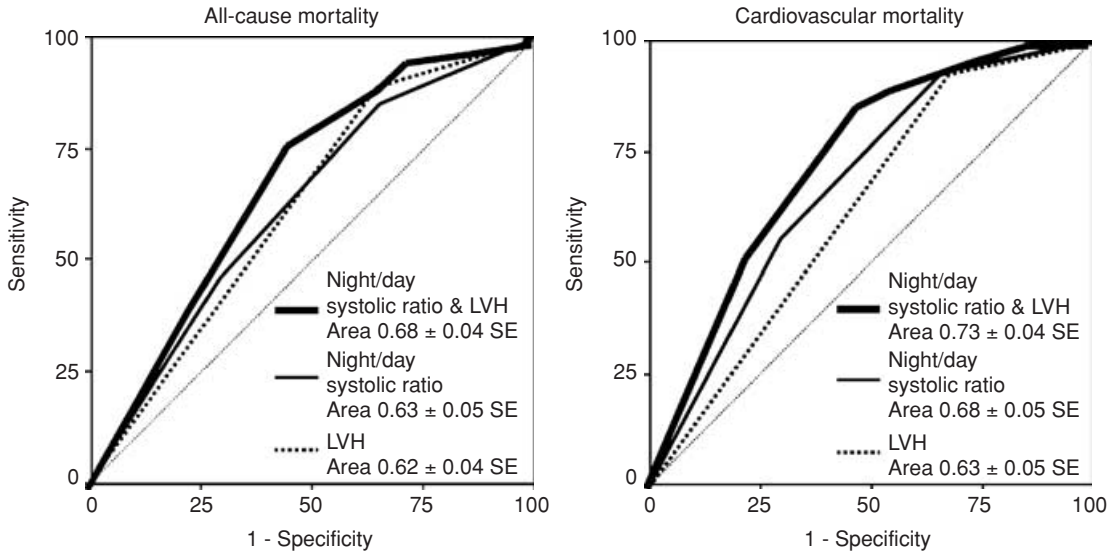

Fig. 1. Receiver operating characteristic (ROC) curves analysis of the night/day systolic ratio and left ventricular hypertrophy (LVH) for all-cause and cardiovascular mortality.

(9%/year) which was by 78% lower than that the average figure in European countries (16%/year) [25].

24-hour ambulatory blood pressure monitoring and cardiovascular risk in dialysis patients

Twenty-four–hour ambulatory blood pressure monitoring is widely used in clinical practice and it is formally incorporated in recent guidelines for the diagnostic, prognostic, and therapeutic evaluation of hypertension [26]. This technique provides not only average estimates of 24-hour blood pressure components but also estimates of blood pressure load during day and night as well as blood pressure variability [27]. The application of 24-hour ambulatory blood pressure monitoring in patients with end-stage renal disease (ESRD) may be of particular interest because these patients frequently show an altered circadian blood pressure profile characterized by a reduced or abolished blood pressure fall during the night [28–30]. In our study the vast majority of dialysis patients displayed arterial hypertension as defined on the basis of specific 24-hour ambulatory blood pressure monitoring guidelines [22], a finding further again emphasizing the pervasive nature of this complication in ESRD. However, we found no significant association between 24-hour systolic, diastolic, and pulse pressure with incident all-cause and cardiovascular mortality. Furthermore, none of predialysis blood pressure components were significantly associated with outcomes. The fact that predialysis blood pressure is not associated with death and cardiovascular events goes along with the observation that none of the diurnal 24-hour ambulatory blood pressure monitoring components (i.e., measurements made in a time frame encompassing predialysis measurements) predicts adverse outcomes. The lack of a significant association between 24-hour ambulatory blood pressure monitoring and incident mortality in our cohort is in apparent contrast with the results emerged in a study by Liu et al [14] where 24-hour ambulatory blood pressure monitoring were inversely associated to incident cardiovascular outcomes. Yet, this relatively small study (80 ESRD patients) included a substantial proportion (39%) of diabetics. The propensity of diabetic uremics for left ventricular disorders and autonomic neuropathy is a most likely confounder for the association between blood pressure and incident cardiovascular events. In the study by Amar et al [15] in 57 dialysis patients both 24-hour systolic and diastolic blood pressure failed to significantly predict cardiovascular mortality after data adjustment for age, gender, and background cardiovascular complications but again this study included diabetics (14%) and patients with previous cardiovascular complications (34%).

Night/day systolic ratio and cardiovascular risk

In the present study, we used the night/day systolic ratio, as an indicator of the night day blood pressure change, because it is well demonstrated that it is the best indicator of the dipping status [21]. We found that nocturnal hypertension (night/day systolic ratio >1) was very common in hemodialysis patients (35%). Quite remarkably this ratio resulted to be the sole blood pressure–derived marker to be associated to all-cause and cardiovascular mortality. The night/day blood pressure fall and the average systolic pressure during night predicted cardiovascular outcomes also in Liu et al [14] and Amar et al [15] studies. Thus, notwithstanding differences in patient characteristics and in indicators of nocturnal blood pressure changes,

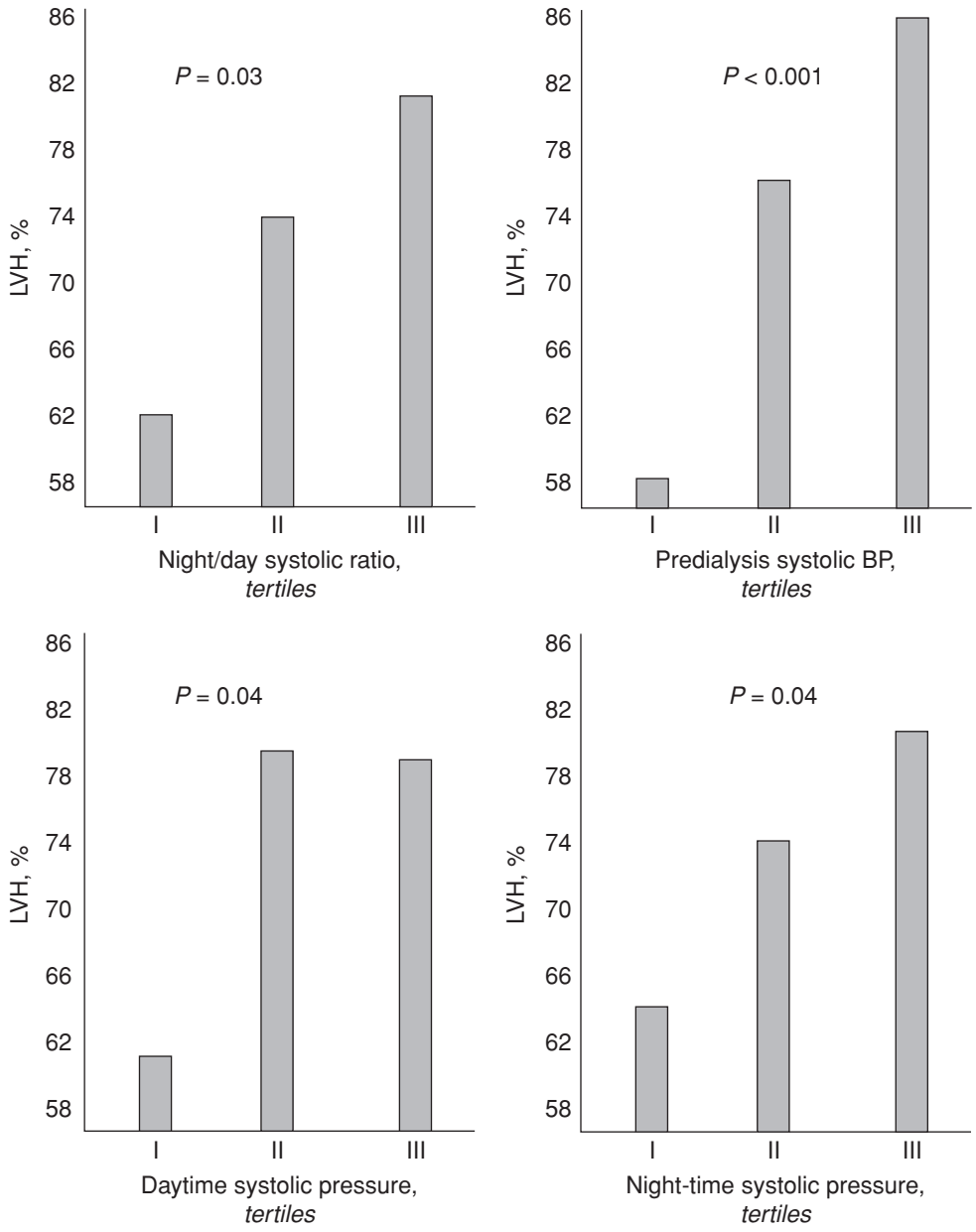

Fig. 2. Relationship between night/day systolic ratio, predialysis systolic pressure, day and night systolic blood pressures with the prevalence rate of left ventricular hypertrophy (LVH). Patients are divided into three tertiles on the basis of individual values of each blood pressure component. Comparisons among groups were made by *P* for trend.

the lack of blood pressure fall during night appears a coherent marker of high cardiovascular risk. In this regard our analysis which modeled the incidence of cardiovascular events on the basis of LVH gives an insight into the sequence of events leading to these outcomes. Indeed, while once again we confirmed that LVH is a strong predictor of all-cause and cardiovascular mortality, the simultaneous inclusion of this risk factor and of the night/day systolic ratio into the same statistical models produces a substantial loss of predictive power of LVH and a less pronounced, yet important, loss of predictive power of the night/day systolic ratio. This statistical phenomenon suggests that the inverted arterial pressure pattern during night-time and LVH are in part in the same causal pathway leading to death and cardiovascular sequelae. The interpretative clue provided by statistical modeling is also fully coherent with the strong, direct relationship between the night/day ratio and left ventricular mass index. Like in previous studies we found that LVH was strongly associated not only with the night/day systolic ratio but also with other 24-hour ambulatory blood pressure components and with predialysis systolic pressure, all

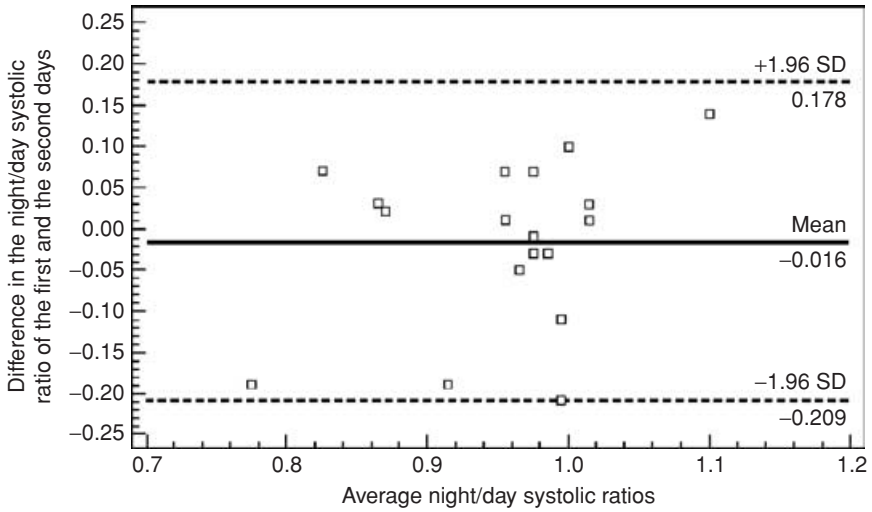

Fig. 3. Bland-Altman analysis of the reproducibility of night/day systolic ratio in a subgroup of 19 hemodialysis patients who underwent 48-hour ambulatory blood pressure monitoring during 2 consecutive days.

associations supporting the contention that arterial hypertension leads to LVH and that in turn LVH is a major pathway mediating the adverse effects of hypertension. However plausible this interpretation, the question remains why the night/day ratio, but not other arterial pressure components, maintains an independent (although weak) relationship with cardiovascular death. We have no direct elements to explain this finding. However, it is likely that the night/day ratio (or the night/day blood pressure difference) is an indicator conveying information beyond arterial pressure. Indeed the night/day systolic ratio but not other blood pressure component is associated with nocturnal hypoxemia [30] and sympathetic overactivity [14] which may per se be conducive to cardiovascular death by LVH-dependent and -independent mechanism. In our study, the largest performed so far and the sole based on a low-risk cohort, the night/day ratio emerges as the sole blood pressure–derived indicator providing prognostic information in ESRD patients. It is interesting to note that the night/day systolic ratio retained a residual predictive power for all cause and cardiovascular death in statistical models, including also LVH and that ROC curve analysis, showed that the prediction power of this ratio is not inferior to that LVH which is currently considered the strongest predictor of cardiovascular complications. This observation suggests that the night day ratio can be used for risk stratification in ESRD patients. ESRD patients with a high night/day systolic ratio should be considered high-risk patients requiring close clinical supervision and intensive treatment of risk factors for cardiovascular disease.

Reprint requests to Professor Carmine Zoccali CNR-IBIM, Istituto di Biomedicina, Epidemiologia Clinica e Fisiopatologia, delle Malattie Renali e dell'Ipertensione Arteriosa, c/o Divisione di Nefrologia - Ospedali Riuniti, Via Vallone Petrara, 89124 Reggio Calabria, Italy.
E-mail: carmine.zoccali@tin.it

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